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The influence of maternal obesity on the long-term health of the offspring

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Abstract

Alongside its immediate implications for pregnancy complications, increasing evidence implicates maternal obesity as a major determinant of health in the offspring during childhood and later adult life. Observational studies provide evidence for effects of maternal obesity on the offspring's risks of obesity, coronary heart disease, stroke, type 2 diabetes and asthma. Maternal obesity may also lead to poorer cognitive performance in the offspring and an increased risk of neurodevelopmental disorders including cerebral palsy. Preliminary evidence suggests potential implications for immune and infectious disease related outcomes. Insights from experimental studies support causal effects of maternal obesity on offspring outcomes, mediated at least in part through changes in epigenetic processes including alternations in DNA methylation, and perhaps through alterations in the gut microbiome. Although the offspring of obese women who lose weight prior to pregnancy have a reduced risk of obesity, to date few controlled intervention studies have reversed maternal obesity and examined the consequences for the offspring. The long term effects of maternal obesity may have profound public health implications and indicate the urgency of studies on causality, underlying mechanisms and effective interventions to reverse the epidemic of obesity in women of child-bearing age and to mitigate its consequences for the offspring.

Introduction

Maternal obesity is widely recognised for its immediate implications in terms of pregnancy complications, including gestational diabetes, pre-eclampsia and delivery of large-for-gestational infants.[1] More recently the recognition that developmental influences can have long term consequences on offspring health and wellbeing has focused attention on the potential for maternal obesity to be one of the influences contributing to the "developmental origins of health and disease".[2] The high prevalence of maternal obesity associated with the global obesity epidemic dictates that determination of any such long-term effects is now an urgent priority.[3]

While control for potentially confounding variables remains a challenge in human observational studies, an extensive experimental literature in rodents and non-human primates has demonstrated that maternal obesity induced by dietary intervention leads to obesity, diabetes, raised blood pressure, fatty liver and behaviour changes in the offspring.[4] Maternal obesity has been shown to permanently alter a variety of metabolic control processes in the fetus, including the hypothalamic response to leptin and subsequent regulation of appetite and pancreatic beta cell physiology.[4] Mechanisms are likely multifactorial but potentially include maternal metabolic changes such as changes in glucose and fatty acids,[5] altered maternal hypothalamic-pituitary-adrenal axis activity[6] and changes in placental function and inflammation.[7]

In this Series paper, we review the evidence linking maternal obesity with long-term offspring consequences, focusing on body composition, cardiometabolic, allergic, immune/infectious and neuro-behavioural outcomes and discuss altered epigenetic

processes as a likely major mechanism underlying long-term effects of maternal obesity on the offspring.

Body composition and cardiometabolic outcomes

An accumulating body of evidence suggests that maternal pre-pregnancy obesity and excessive gestational weight gain are associated with an increased risk of obesity in the offspring during childhood.[8-11] While the initial focus was on extreme categories of maternal obesity, several recent studies suggest that higher maternal pre-pregnancy body mass index (BMI) across the full spectrum is associated with greater childhood adiposity and an adverse body fat distribution.[12-15] Higher gestational weight gain is also associated with a higher childhood BMI and greater fat mass estimated by dual-energy X-ray absorptiometry.[15-20] Whilst both maternal pre-pregnancy obesity and excessive gestational weight gain seem to be associated with a higher blood pressure, adverse lipid profile, and insulin resistance in childhood,[12,16,20,21] there is some evidence that these associations are largely mediated by childhood BMI.[12,16]

Alongside studies focused on outcomes in children, multiple studies have suggested that a higher maternal pre-pregnancy BMI and greater gestational weight gain are associated with a higher BMI in adolescents and adults.[22-29] A study of 2,432 Australians found that greater maternal gestational weight gain was associated with a higher BMI (on average 0.3 kg/m^2 (95% CI 0.1-0.4 kg/m^2) higher for each 0.1 kg/week greater gestational weight gain) in the offspring at the age 21 years.[29] These associations were independent of maternal pre-pregnancy BMI. Similarly, a study among 1400 mother-offspring pairs in Jerusalem showed that higher maternal pre-pregnancy BMI was associated with higher offspring BMI at age 30 years (an increase of 1.8kg/m^2 in offspring BMI per increase of one standard deviation in

maternal pre-pregnancy BMI).[23] In this study the associations of maternal pre-pregnancy BMI with cardiovascular risk were fully explained by adult BMI.[23] Findings from the Helsinki Birth Cohort Study (HBCS) suggest that maternal BMI is positively associated with offspring BMI at age 60 years.[30,31] A higher maternal BMI was also associated with a less favourable body fat distribution in female offspring at a mean age of 62 years.[31] Similarly to the studies in children, no consistent associations of maternal BMI with other cardiovascular risk factors were present among adults. Inconsistencies may be due to study design and availability of measurements and confounding factors.

Findings from registration/register-based and retrospective cohort studies in Helsinki implicate maternal obesity in pregnancy as an important determinant of the risk of cardiovascular morbidity and mortality in the offspring. A further study using birth records from 37,709 individuals in the UK showed that a higher maternal BMI was associated with an increased risk of premature all-cause mortality (hazard ratio HR 1.35, 95% CI 1.17-1.55) and hospital admissions for cardiovascular events in adult offspring (HR 1.29, 95% CI 1.06-1.57).[32] These associations were independent of socioeconomic status and current age. In line with these findings, similar findings have been reported in the Helsinki Birth Cohort Study participants born 1934–44 and followed up between the years 1971 to 2010.[33] Cardiovascular disease, coronary heart disease, type 2 diabetes and stroke were all more common among offspring of obese mothers. For cardiovascular disease, findings were similar for males and females, while for type 2 diabetes the association was stronger in women. The association of maternal BMI with offspring coronary heart disease was statistically significant among males only (trend per kg/m^2 HR 1.031, 95% CI 1.009-1.054), whereas the association of maternal BMI with stroke was significant among females only (trend per kg/m^2 HR 1.059, 95% CI 1.019-1.101).[33]

Several studies have aimed to identify critical periods of maternal weight during pregnancy for childhood outcomes. A study performed among 5,000 UK mother-offspring pairs showed that gestational weight gain in the first 14 weeks of pregnancy was positively associated with offspring adiposity at 9 years of age.[17] Likewise a study among 6,000 Dutch mother-offspring dyads showed that early-pregnancy weight gain was associated with an adverse cardio-metabolic profile (OR 1.20 95% CI 1.07- 1.35) in childhood[16] and that this finding was independent of maternal weight gain before pregnancy and of weight gain in later pregnancy. These studies suggest that maternal weight gain in early pregnancy, when maternal fat accumulation forms a relatively large component of gestational weight gain,[34] may be a critical period for an adverse childhood cardiovascular risk profile.

Thus, maternal pre-pregnancy obesity and gestational weight gain, especially in early pregnancy, may influence the risks of adiposity and adverse cardiovascular risk from childhood to adulthood.

Allergic and atopic outcomes

The global rise in maternal obesity has been implicated in the parallel rising burden of asthma, allergic disease and other early immune diseases, with speculation that this may be part of the multisystem consequences of obesity-related inflammation for the offspring. Indeed, a recent meta-analysis that included 14 studies and 108,321 mother-child pairs found that maternal overweight or obesity in pregnancy were associated with increased risks of childhood asthma or wheeze ever (OR 1.31, 95%CI 1.16-1.49) and current asthma or wheeze (OR 1.21; 95%CI, 1.07-1.37), independent of offspring BMI.[35] Higher maternal

gestational weight gain was also associated with higher offspring odds of current asthma or wheeze (OR 1.015 per 1 kg increase, 95% CI 1.01–1.02) but not associated with asthma or wheeze ever (OR = 1.04 per kg, 95% CI 0.97–1.11). Follow up of the Danish National Birth Cohort found that the impact of maternal obesity was largely limited to asthma and wheezing, and did not increase the risk of eczema, sensitisation (largely assessed to aeroallergens) or hay fever,[36] suggesting tissue specific effects. This is consistent with evidence that allergic diseases result from both systemic immune dysregulation and tissue-specific effects during critical stages of development.

Whilst pathways linking maternal obesity to offspring allergic and atopic outcomes are multifactorial, the contribution of reduced microbial diversity, and in particular intestinal dysbiosis, has emerged as a central risk factor. Changing microbial exposure has been long implicated in the dramatic increase in early-onset inflammatory non-communicable disease such as allergy and asthma, but the importance of these complex microbiological ecosystems is becoming increasingly apparent in the physiological, immunological, and metabolic dysregulation seen in obesity.[37] Emerging evidence suggests the multisystem influences of declining microbial diversity also begin in utero, including through epigenetic influences.[38]

Thus, an aberrant gut microbiome, known to be associated with maternal obesity, provides an additional mechanism for both the immune and metabolic consequences on the developing fetus.[39] There is preliminary evidence in humans that dietary manipulation of the maternal microbiome in pregnancy with prebiotic fibre has beneficial effects for both offspring immune function and metabolism (reviewed in [40]). In animal models this can prevent the development of an allergic asthma phenotype in the offspring – an effect

directly mediated by the short chain fatty acid (SCFA) metabolites produced by microbial fermentation of dietary fibre.[41] In addition to their effects on metabolism, glucose homeostasis and appetite regulation, SCFA also have powerful anti-inflammatory effects – both in local tissues and systemically through regulatory T cell induction.[40,41] Notably, this includes tissue-specific effects in the lung. Moreover, there is preliminary evidence in humans that high SCFA (acetate) levels in pregnancy correlates with fewer doctor visits for cough and wheeze in their offspring.[41] This provides a novel perspective on how a Western-style fast food diet associated with obesity might increase asthma risk, whereas a Mediterranean diet (high in fish, fruits, nuts and vegetables) might be protective against wheeze and asthma in childhood[42]; such an effect could be mediated, at least in part, through the microbiome and its metabolic effects on immune responses and tissue function.

Collectively these observations underscore the complex interplay between evolving metabolic and immune responses and how these may be modified by maternal nutrition, adiposity and microbial diversity to alter susceptibility to inflammatory diseases across the lifecourse.[43]

Other immune and infectious disease related outcomes

Whether maternal obesity increases offspring susceptibility to other immune and infectious disease related outcomes has been less well studied, but is important to consider given the rising increases in obesity in low- and middle-income countries[44] where the burden of infection during pregnancy and in childhood is high. With dampened maternal immunity to tolerate the semi-allogenic offspring, pregnancy represents a period of increased susceptibility to infection, and maternal obesity further increases this risk.[45] Studies in

rodent models of maternal obesity demonstrate worse offspring outcomes in response to bacterial infection and experimentally induced autoimmunity.[46,47]

In humans, maternal obesity also impacts the maturation and development of the newborn immune system, with adverse influences on the frequency and function of key innate and adaptive immune cells measured in umbilical cord blood.[48]   Infants born in developed countries also have different proportions of circulating immune cells and innate immune responses compared to those born in developing countries, but at present little is known about the contributions of maternal nutritional state vs. other exposures (e.g. infections) to these differences.[49] The difference may, however, have important effects on susceptibility to pathogens, responses to vaccines, and development of immunopathological disorders such as asthma and allergy.[50] Obesity is a recently recognised risk factor for severe viral infections,[51] and in obese mothers prenatal exposure to a range of infections (such as influenza, Toxoplasma gondii, rubella, cytomegalovirus and herpes simplex virus) could have consequences for the offspring, including cardiometabolic and neurobehavioural diseases. It is not known if maternal obesity further increases susceptibility to vertical transmission of pathogens, though it is plausible that this may occur indirectly through exacerbation of the already altered maternal endocrine, immune, metabolic milieu and inflammatory status associated with maternal adiposity.[52,53]

A further important consideration is whether therapies used to treat maternal infection can also have adverse impacts on the offspring's risk of later disease, through increasing maternal adiposity. Notably protease inhibitors, antiretrovirals (ARVs) used to prevent mother-to-child transmission of HIV, are associated with adverse maternal metabolic side effects. These include changes in maternal body composition including increased central

adiposity, together with associated dyslipidaemia, insulin resistance, type 2 diabetes and mitochondrial toxicity which may have long term effects on ARV-exposed infants.[54] Detailed studies will be required to establish the long term effects, and to determine optimal regimens to reduce any adverse outcomes.

Offspring neurocognitive and behavioural outcomes

Despite the potential public health importance, relatively few cohort studies have examined associations between maternal obesity and detailed neuro-developmental outcomes in offspring (Table 1). For cognitive outcomes, human data showed that higher *pre-pregnancy* weight is associated with poorer cognitive outcomes, while higher (but not excessive) weight gain *during* pregnancy has been associated with better offspring cognitive outcomes.[55,56] However, published data do not allow definitive conclusions of potential effects of *pre-pregnancy* adiposity on offspring cognitive development. Most studies found modest inverse associations with both early and later cognitive standardized assessments or reading and math scores,[57] while a recent study found indications for a possible temporary increase in cognitive outcomes on a standardized assessment at 6 months.[58] However, associations with maternal reports of cognitive performance were inconsistent in other large cohort studies.[59]

Maternal obesity has also been associated with offspring behavioural and emotional problems.[57,60] A recent meta-analysis and longitudinal study found an increased risk for Autism Spectrum Disorders in children of mothers with obesity before/during pregnancy or excessive gestational weight gain,[60,61] with other approaches suggesting a particularly robust association for excessive gestational weight gain .[62] In 3 large European cohort studies the association between pre-pregnant obesity and Attention Deficit Hyperactivity

Disorder was inconsistent, and lost when adjusted in full sibling comparisons.[59,63] Fewer studies have investigated the association with affective disorders and no recent studies have investigated the link with anxiety, psychotic or eating disorders. Only one qualitative review has been published on pre-pregnancy obesity and schizophrenia, which suggested an association, although maternal schizophrenia was not taken into account.[64] Although past studies reported contradictory results relating maternal obesity to offspring cerebral palsy,[65] large studies over the last 5 years have found positive associations, even after multiple adjustments.[57]

One major limitation of the above-mentioned studies is the difficulty in differentiating intrauterine effects from residual confounding. One way to explore this is to compare effect sizes of maternal obesity versus paternal obesity. However, even with maternal effect sizes, it is clear that other influences are also associated with both obesity and neurodevelopment, such as maternal intelligence, socio-economic status, breastfeeding, maternal mental health, maternal diet and other postnatal lifestyle influences. Other reasons for contradictory findings are differences in methodology, sampling biases, different ages of measuring outcomes and differences in defining obesity and outcomes. Some studies used retrospective self-reports of pre-pregnancy weight or maternal reports of offspring outcomes, which may be less reliable.[55,59]

In human studies it is difficult to confirm causation or to identify mechanisms linking maternal obesity with offspring neurodevelopment. However, studies in rodents and non-human primates have indicated 3 potential pathways: 1) high levels of nutrients, including fatty acids and glucose; 2) high levels of hormones like leptin and insulin; 3) inflammatory mediators, including interleukins and tumor necrosis factor.[57,66] These factors cross the

placenta and can influence fetal neuroendocrine development, neuronal proliferation and brain development.[57,66] Many dynamic factors play a role, with complex interactions between maternal environment, placental patho-physiology and fetal epigenetic changes. Indeed, animal studies showed that obesity during pregnancy can change brain homeostasis and offspring behaviour through epigenetic mechanisms, including in the serotonin and dopamine pathways, lipid peroxidation and corticosteroid receptor expression.[67,68] Even parental lifestyle factors prior to and at conception may have transgenerational effects by epigenetic reprogramming at fertilization.[69]

Maternal obesity has many pathophysiological features in common with gestational diabetes, a condition increasingly associated with evidence of mild cognitive impairment in the offspring.[58] For maternal obesity the paucity of current evidence indicates a need for large-scale studies with more detailed cognitive and behavioural phenotyping in populations of different cultures and ethnicities. Future studies should examine if maternal diet or obesity itself is more important for programming of neurodevelopmental outcomes, and include comprehensive assessments of diet and direct measurements of adiposity. Moreover, underlying mechanisms should be studied in humans with biomarkers including genetic and epigenetic modifications.

Epigenetic modifications: a potential underlying mechanism

Epigenetic processes are emerging as an important mechanism through which the "memory" of developmental exposures is held, with pathophysiological consequences for a variety of organs and systems. Epigenetic modifications have been proposed as a key causal mechanism linking maternal adiposity and offspring outcome.[70] Moreover, there is

now emerging evidence that epigenetic processes can act over several generations, including three or more generations and through the paternal line.[71] Epigenetic modifications result in alterations in gene function in the absence of changes in the DNA sequence. The epigenetic marks which mediate this include DNA methylation, post-translational modification of histones and non-coding RNAs. DNA methylation occurring predominantly at cytosines in cytosine-guanine (CpG) dinucleotides is the most widely studied. Table 2 summarises the existing evidence linking maternal obesity in humans with offspring DNA methylation.

As shown in Table 2, a number of studies have used global methylation techniques to explore associations between maternal obesity and offspring DNA methylation. Though the findings are not consistent, three cohort studies found associations between maternal BMI and offspring DNA methylation at birth[72,73] and at 3 years.[74] Notably, in the largest and methodologically most robust study[73] the methylation differences were only observed with comparisons of extreme groups of BMI (i.e. obese vs normal-weight) and not when the over-weight group was compared with normal-weight group. Reasons are unknown but this observation may partly explain the negative findings in other studies where analyses have been conducted across a range of maternal BMI measurements.[75,76] The observation of differentially methylated CpG sites in the peripheral blood of 2-25 year old siblings born to obese mothers before and after bariatric surgery with associated weight loss[77] is also consistent with the hypothesis that maternal obesity impacts on offspring DNA methylation.

Where a candidate gene approach has been adopted, associations between maternal adiposity and DNA methylation at imprinted genes[78-80] or in a number of genes known to be involved in metabolism[78-82] have been reported. Of particular interest is the observation that aryl-hydrocarbon receptor repressor (AHRR) DNA methylation is 2.1% higher in offspring of

obese vs. normal weight mothers[81]; robust links are now established between maternal smoking and offspring AHRR methylation and there is much evidence that maternal smoking is associated with long term effects on offspring adiposity.[15] The observations raise the possibility that AHRR DNA methylation may be involved in the link between maternal obesity and offspring adiposity. There is also evidence that maternal glycaemia is involved in causal pathways influencing offspring leptin epigenetic regulation.[83]

Methodological considerations

Fixed genetic variants shared by mother and offspring are important confounders of proposed links between metabolic factors linked to maternal obesity and offspring outcomes, as are shared postnatal influences on diet/lifestyle behaviours[84] and microbiome-related mechanisms.[85] However, abdominal fat depots already differ at birth between groups with different risks of later metabolic disease[86] and it seems likely that at least some of the effects of maternal obesity are mediated through prenatal environmental mechanisms. Further delineation of maternal effect modifiers will aid the development of interventions to improve offspring health, as will understanding of the underlying mechanisms and related biomarker signatures of these processes. Alongside giving insights into the fundamental processes and additional risk factors, such signatures will provide immediate outcome/adherence measures for interventions, and enable identification of postnatal effect modifiers and stratification of infants for targeting of postnatal interventions.

Whilst the available data is consistent with the hypothesis that maternal obesity impacts on offspring DNA methylation changes at birth, whether these changes impact on development of later adverse outcomes in the offspring remains unclear. The observation that the

methylation changes found at birth were also present at 3 year follow-up,[74] provides some evidence that the methylation changes may persist over time. This, together with the observation of persistence of epigenetic marks associated with obesity across childhood and adolescence,[87] raises the possibility that epigenetic analysis may provide useful biomarkers of disease risk across the lifespan. The findings do need to be interpreted with caution. Few studies have included attempts to replicate or validate findings through using a replication cohort,[76] validation in comparison with published data[73] or sex specificity. It is well established that many DNA methylation patterns are tissue- and cell- specific,[88] so the relevance of findings from DNA extracted from cord or peripheral blood leukocytes remains unclear. However, there is also evidence that, for a number of non-imprinted genes, DNA methylation levels measured in blood are equivalent in buccal cells despite the fact that these cell types arise from different germ layers (mesoderm and ectoderm respectively).[89]

Whilst the majority of studies have utilised DNA extracted from blood leukocytes as a window on processes occurring in the fetus,[72-76,78-81] the heterogeneity in sample population, study size, and the inconsistency between methodological approaches, makes comparison of studies challenging. Further, methodological considerations, particularly if complex tissues are used such as the placenta which contains mixed cell types, each with a distinct methylation pattern, may present problems with data interpretation.

We do not know whether the reported associations between maternal obesity and epigenetic processes are causal in relation to later outcomes, or whether they are merely a response to the maternal obesogenic environment, or are secondary to the changes in growth that occur in a fetus exposed to maternal obesity in utero. Obesity is also associated with changes in intestinal microbiota and epigenetic changes can also be induced by gut

microbiome metabolites such as short chain fatty acids. Obesity associated changes in intestinal microbiota have implications for infant microbiome development with consequences for later child outcomes.[90] Postnatal colonization of the microbiome in offspring has been linked to changes of the hypothalamic-pituitary-adrenal axis linking brain function and intestinal bacteria.[91] Studies indeed showed associations between changes in the microbiome and neurodevelopment disorders in which inflammation is implicated, such as autism-spectrum disorders and attention-deficit hypersensitivity disorder.[92]

Studies to test causality for effects of maternal obesity on offspring epigenetics in humans are hard to conduct; however, utilising associations with paternal obesity as a 'negative control', the demonstration that epigenetic modifications are more strongly associated with maternal than paternal obesity[73] provides some support for the thesis that the associations of maternal obesity with offspring methylation are due to an intrauterine mechanism. The experimental demonstration that paternal diet prior to conception can have lasting effects on offspring outcomes through epigenetic processes does, however, add further complexity to an already complex situation.[69] Further, many of the techniques used to investigate global DNA methylation changes are limited in coverage of the human epigenome. For example, the Infinium HumanMethylation450 BeadChip array used in many recent studies[73,77] only covers around 1.7% of all CpG sites in the genome and to date there has been little consideration of non-CpG methylation or 5-hydroxymethylation.[93] More studies are needed that consider interaction of epigenetic changes with changes in the genome – recent studies suggest that around a quarter of the variation in neonatal methylomes arises from fixed genetic variants, with the remainder from gene-environment interactions.[94]

Conclusion

Although initial research linking developmental influences with major non-communicable disorders in later life focused on the effects of fetal undernutrition, increasing evidence indicates that exposure to maternal obesity also leads to an increased risk of disease in the offspring. Observational studies have provided strong evidence for associations between maternal obesity and an increase in the offspring's risk of obesity, coronary heart disease, stroke, type 2 diabetes and asthma. Emerging evidence suggests that maternal obesity may be associated with poorer cognition in the offspring and an increased risk of neurodevelopmental disorders including cerebral palsy. With the exception of recent small studies of obese women who had bariatric surgery between pregnancies, there is a paucity of controlled intervention studies that have reversed maternal obesity and examined the consequences for the offspring. However, the offspring of obese women who lose weight prior to pregnancy have reduced risk of obesity[95], and insights from experimental studies support a causal effect of maternal obesity on offspring outcomes in later life. Mechanistic insights also support causal effects on maternal obesity on the offspring, mediated through changes in epigenetic processes, and perhaps through alterations in the gut microbiome of the offspring. Table 3 lists key points for further research.

Greater insight is needed into the mechanisms acting in the mother, through which maternal obesity and excess nutrient supply impart increased risk for future metabolic disease. Pre-pregnancy obesity predisposes the mother to gestational diabetes, hypertension and pre-eclampsia which may affect placental function and fetal energy metabolism. In addition, obesity in pregnancy is associated with complex neuroendocrine,

metabolic and immune/inflammatory changes which likely impact on fetal hormonal exposure and nutrient supply.[6,96]

The observations linking maternal obesity with lifelong consequences for the offspring have profound public health implications. The prevalence of overweight/obesity in women of childbearing age is increasing worldwide (with over 60% of women either overweight or obese at conception in the United States[97]), which will increase population of children exposed to an "obese intrauterine environment" and thus perpetuate cycle of increasing obesity and chronic disease burden. Public health measures that will rapidly reverse the current epidemic of maternal obesity appear implausible at present; in their absence, breaking the cycle of maternal and offspring obesity requires from a new generation of intervention studies, based on more detailed analysis of observational studies and designed with a better understanding of the underpinning mechanisms acting in the mother and offspring.

Search strategy

In this section we systematically reviewed studies with MEDLINE (1980-2015, EMBASE (1980-2015) and Cochrane library (1980-2015) with the search terms "maternal obesity", "pre-conception", "pregnancy", "intergenerational", "offspring" or "infant" or "child" in combination with the terms "fetal programming", "epigenetic", "methylation", "disease", "immunity", "cardiovascular", "type 2 diabetes", "infection", "HIV", "malaria", "proinflammatory", "cognition", "school performance", "psychopathology", "mental health", "ADHD", "autism", "affective disorders", "anxiety disorders", "eating disorders", "psychotic disorders" and "cerebral palsy". We selected large cohort and case-control studies that were judged relevant, with a focus on studies conducted over the last 10 years in humans,

but not excluding commonly referenced and highly regarded older publications. We also included references of articles identified by our search strategy and included those that were found relevant.

Conflict of interest statement

KMG reports other from Nestle Nutrition Institute, grants from Abbott Nutrition & Nestec, outside the submitted work; in addition, KMG has a patent Phenotype prediction pending, a patent Predictive use of CpG methylation pending, and a patent Maternal Nutrition Composition pending. SLP reports other from Danone Scientific Advisory Board, other from Nestle Nutrition Institute Scientific Advisory Board, other from ALK Abello, outside the submitted work. The other authors have nothing to disclose.

Authors' contributions

All authors each drafted parts of the Series paper, which were subsequently integrated by KMG and RMR. The final version of the manuscript was corrected where needed and approved by all authors.

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Table 1. Studies linking maternal obesity with offspring asthma

Study	Population	Sample Size & Age	Country	Major Findings
Dumas, et al. Allergy 2016 – in press	Analyses of children of participants in the Nurses' Health Study II. Physician-diagnosed asthma and allergies were assessed by questionnaires.	n=12,963 children aged 9-14 years	USA	Maternal pre-pregnancy overweight (OR: 1.19, 95% CI: 1.03-1.38) and obesity (1.34, 1.08-1.68) associated with asthma in offspring. Gestational weight gains (GWG) of <15 lb and higher risk of offspring asthma (1.28, 0.98-1.66)
Pike, et al. Thorax 2013; 68: 372-379.	Mothers and children from the Southampton Women's Survey. Childhood follow-up visits occurred at 6, 12, 24 and 36 months. Skin prick tests at 6 years.	n=940 children with data in the first 6 years	UK	Greater maternal BMI and fat mass associated with increased transient wheeze (relative risk (RR) 1.08 per 5 kg/m^2, p=0.006; RR 1.09 per 10 kg, p=0.003), but not with persistent wheeze or asthma. Maternal adiposity not associated with offspring atopy, exhaled nitric oxide.
Guerra, et al. Paediatr Perinat Epidemiol 2013;27: 100-108.	Multicentre longitudinal population-based study using two INMA birth cohorts in Sabadell/Gipuzkoa. Wheeze data obtained through interviewer-administered parental questionnaires.	n=1107 mother–child pairs assessed up to 14 months	Spain	Maternal prepregnancy obesity increased risk of frequent [RR 4.18, 95% CI 1.55, 11.3] but not infrequent (RR 1.05 [95% CI 0.55, 2.01]) wheezing in their children. Children of obese mothers more likely to have frequent wheezing than children of normal-weight mothers (11.8% vs. 3.8%; P = 0.002).
Harpsoe, et al. J Allergy Clin Immunol 2013;131:1033-1040.	Mother-child pairs from the Danish National Birth Cohort with information from the 16th week of pregnancy and at age 6 months, 18 months, and 7 years of the child	n=38,874 mother-child pairs assessed up to 14 months	Denmark	Maternal prepregnant BMI>/=35 (adjusted OR, 1.87; 95% CI, 0.95-3.68) and GWG>/=25 kg (adjusted OR, 1.97; 95% CI, 1.38-2.83) were associated with current severe asthma at age 7 years. Maternal BMI and GWG were not associated with eczema or hay fever.
Watson, et al. Maternal Child Health 2013; 17: 959-967.	Prospective study of European & Polynesians from northern New Zealand. Home assessments in pregnancy & age 18 months.	n = 369 18 month old infants	New Zealand	Changes in subcutaneous fat during pregnancy are associated with prevalence of infant wheeze. Wheeze prevalence was 19.2% where the difference in mothers' skinfolds between months 4 and 7 decreased by ≥10 mm and 41.7% where the difference increased by ≥10 mm.
Patel, et al. J Epidemiol Community Health 2012;66: 809-814.	Adolescents born within the prospective 1986 Northern Finland Birth Cohort	n=6945 adolescents assessed for asthma symptoms age 15-16 yrs	Finland	High maternal pre-pregnancy BMI was a significant predictor of wheeze in the adolescents (increase per kilogram per square metre unit; 2.8%, 95% CI 0.5 to 5.1 for wheeze ever; and 4.7%, 95% CI 1.9 to 7.7 for current wheeze).

Lowe, et al. J Allergy Clin Immunol 2011;128: 1107-1109.	Data linkage of Swedish national registers: Swedish Medical Birth Registry, Swedish Prescribed Drug Register and Swedish Inpatient Registry. Asthma medication use from ages 6 to 8 years and 8 to 10 years	n=89,783 children born to 129,239 mothers in Stockholm between 1998 and 2009.	Sweden	Higher maternal BMI was consistently associated with an increased risk of asthma in the child, both in terms of medicine use and hospitalization. Risk of asthma medication use increased for Maternal BMI of 30-34.9 (OR: 1.40, 95% CI: 1.16-1.68) and Maternal BMI of >35 (OR: 1.57, 95% CI: 1.15-2.15)
Scholtens, et al. Int J Obes 2010; 34: 606-613.	Birth cohort participating in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, with sensitization and bronchial hyperresponsiveness determined at 8 years	n=3963 children and their mothers	Netherlands	Maternal overweight before pregnancy increased risk of childhood asthma at 8 years (OR=1.52, 95% CI: 1.05-2.18) in children with atopic heredity. No association was observed in children without a predisposition (OR=0.86, 95% CI: 0.60-1.23). There was no association with sensitization or BHR.
Kumar, et al. Pediatr Allergy Immunol Pulmonol 2010;23: 183-190.	Boston Birth Cohort (started in 1998) followed prospectively to a mean age of 3.0 +/- 2.4 years with study visits aligned with the pediatric primary care schedule.	n=1,191 children	USA	Children of obese mothers had an increased risk of recurrent wheezing (OR, 95% confidence interval: 3.51, 1.68-7.32). In contrast, maternal obesity was not associated with eczema or food allergy
Haberg, et al. Paediatr Perinat Epidemiol 2009;23: 352-362.	Population-based cohort study: Norwegian Mother and Child Study (MoBa).	n=33,192 children, born between 1999 and 2005	Norway	The risk of wheeze increased linearly with maternal BMI in pregnancy, and was 3.3% higher [95% CI 1.2, 5.3] for children with mothers who were obese during pregnancy, than for children of mothers with normal BMI.
Reichman, et al. Matern Child Health 2008 12: 725-733.	Population-based sample of children born in large U.S. cities in 1998-2000. Main outcome: maternal reported diagnosis of asthma in child by 3 years.	n=1971	USA	Children with obese mothers had 52% higher odds of having an asthma diagnosis by age 3 (OR=1.52; 95% CI: 1.18-1.93).

Table 2. Studies reporting the odds ratios of neurodevelopment disorders in offspring for women with overweight or obesity before or during pregnancy. Only studies over the last 6 years, with reported odds ratios have been included.

Studies using global methylation techniques						
Study	Population	Design	Country	Age	Overweight/obesity mother	Odds ratios of Neurodevelopment Disorders
Brion, et al. Pediatrics 2011;127:e202-211.	British Avon Longitudinal Study UK and Generation R study in the Netherlands n=5000 (UK) and n=2500 (the Netherlands)	Cohorts	The Netherlands and the UK	Behavioral problems, e.g. attention deficit measured at 47 months (UK) and 36 months (Netherlands) by parental reports	Maternal pre-pregnancy overweight (25≤BMI<30)	Maternal pre-pregnancy overweight was not associated with an increased risk of attention deficit problems (or other emotional problems and internalizing problems) found in both cohorts.
Chen, et al. Int J Epidemiol 2014; 43: 83-90.	Population based cohort study with data of national and regional registers n=673,632 with n = 272,790 full biological siblings	Cohort	Sweden	From age 3 until diagnosis of ADHD, death or emigration	Pre-pregnancy overweight (25≤BMI<30) and pre-pregnancy obesity (BMI ≥30)	Pre-pregnancy overweight associated with OR = 1.23, (95% CI = 1.18-1.27) increase in Attention Deficit Hyperactivity Disorder & OR = 0.98 (95% CI = 0.83-1.16) non-significant increase in full sibling comparisons. Pre-pregnancy obesity associated with OR 1.64 (95% CI = 1.57-1.73) increase in ADHD & OR 1.15 (95% CI = 0.85-1.56) non-significant increase in full sibling comparisons for ADHD.
Crisham, et al. J Pediatrics 2013; 163: 1307-1312.	Longitudinal population based study n = 6,221,001 with 8798 diagnoses of Cerebral Palsy	Cohort	USA	Newborns followed up until age 5 for Cerebral Palsy assessment	Pre-pregnancy obesity (BMI >=30) and pre-pregnancy morbid obesity (BMI ≥40)	Pre-pregnancy obesity was associated with OR 1.72 (95% CI 1.25-2.35) increase in Cerebral Palsy. Pre-pregnancy morbid obesity was associated with OR 3.79 (95% Ci 2.35-6.10) increase in Cerebral Palsy.
Gardner, et al. Int J Epidemiol 2015; 44: 870-883.	Stockholm Youth Cohort, population-based study	Cohort	Sweden	4 years to 21 years	Pre-pregnancy overweight (25≤BMI<30) and pre-pregnancy	Pre-pregnancy overweight was associated with OR 1.31 (95% CI 1.21-1.41) increase in Autism Spectrum Disorders.

	n = 333,057 with 6,420 Autism Spectrum Disorder cases and 1,156 matched siblings				obesity (BMI ≥30) and Excessive gestational weight gain (according to the Institute of Medicine)	Pre-pregnancy obesity was associated with OR 1.94 (95% CI 1.72-2.17) increase in Autism Spectrum Disorders. Excessive gestational weight gain was associated with OR 1.48 (95% CI 0.93-2.38) non significant increase in Autism Spectrum Disorders in matched sibling analyses.
Jo, et al. Pediatrics 2015; 135: e1198-1209.	Infant Feeding Practices Study II, a US national distributed longitudinal study n = 1311	Cohort	USA	6 years	Severe pre-pregnancy obesity (BMI >35.0)	Severe pre-pregnancy obesity was associated with OR 3.13 (95% CI, 1.10-8.94) increase in Autism Spectrum Disorders/development delay disorders diagnosis and with OR 4.55 (95% CI, 1.80-11.46) increase in ADHD by maternal report.
Li, et al. J Autism Devel Disorders 2016; 46: 95-102	Meta-analysis of 4 population-based and 1 case-cohort study n =129,733 with 924 Autism Spectrum Disorder cases (Canada); n = 517 with 315 Autism Spectrum Disorder cases (USA); n = 4800 with 100 Autism Spectrum Disorder cases (USA); n = 92,909 with 419 Autism Spectrum Disorder cases (Norway); n = 62 with 14 ASD cases (USA case-control study)	4 population-based cohort and one case-cohort study	1 from Canada, 3 from USA, and 1 from Norway	1-17 years (Canada) 4-5 years (USA) 2 years (USA) 4-13.1 years (Norway) 2-5 years (USA, case-control study)	Pre-pregnancy obesity and obesity during pregnancy (BMI ≥30 or pre-pregnancy weight ≥90 kg)	Pre-pregnancy and pregnancy obesity was associated with a pooled *adjusted* OR 1.47 (95% CI 1.24-1.74) increase in Autism Spectrum Disorders.

| Pan, et al. J Child Neurol 2014; 29: NP196-201. | South Carolina Medicaid program, a retrospective study n=83,901 with 100 cases of any Cerebral Palsy and 53 cases of confirmed Cerebral Palsy (at least 2 diagnoses) | Cohort | USA | 5 - 8 years | Severe obesity at birth (35≤BMI<40) and morbid obesity at birth (BMI ≥40) | Severe obesity was associated with OR 2.00 (95% CI 1.00 – 4.01) increase with any Cerebral Palsy and OR 1.22 (CI 0.38-3.81) with confirmed Cerebral Palsy. Morbid obesity was associated with OR 2.95 (95% CI 1.45-5.97) increase in any Cerebral Palsy and OR 3.03 (CI 1.09-8.37) with confirmed Cerebral Palsy. |
| Roderiquez, et al. J Child Psychol Psychiatr 2010; 51: 134-143. | Population-based prospective pregnancy-offspring study n =1714 | cohort | Sweden | 5 years | Pre-pregnancy overweight (25≤BMI<30) and Pre-pregnancy obesity (BMI ≥30) | Pre-pregnancy overweight was associated with OR 1.92 (95% CI 1.21-3.05) significant increase in ADHD by teacher ratings and OR 1.37 (95% CI 1.07-1.75) non-significant increase in high inattention symptom score by maternal ratings. Pre-pregnancy obesity was associated with OR 2.05 (95% CI 1.06-3.95) increase in ADHD symptoms by teacher ratings and OR 1.89 (95% CI 1.13 – 3.15) increase in ADHD symptoms by maternal ratings. |

Table 3. Human studies linking maternal obesity with DNA methylation changes in the offspring

Studies using global methylation techniques						
Study	**Population**	**Design**	**Country**	**Tissue**	**Method**	**Findings**
Michels, et al PLoS One. 2011; 6: e25254.	Epigenetic Birth Cohort 319 newborns with 316 placentas	cohort	USA	Cord blood Placental tissue	Global methylation using a LINE-1 bisulfite pyrosequencing assay	No associations between maternal prepregnancy BMI and global methylation in either tissue.
Herbstman et al. PLoS One. 2013; 8: e72824	Northern Manhattan Mothers & Newborns Study of the Columbia Center for Children's Environmental Health n=279 newborns with n=165 at 3 year follow-up.	cohort	USA	Cord blood Peripheral blood at 3 years	Global DNA methylation using the Methylamp™ Global DNA Methylation Quantification Kit (Epigentek Group Inc, NY).	Pre-pregnancy BMI was negatively predictive of both cord and three-year DNA methylation.
Morales, et al BMC Res Notes. 2014; 7: 278.	Avon Longitudinal Study of Parents and Children (ALSPAC) Cohort; n=88 term newborns. Replication study population including 170 term newborns born	cohort	UK	Cord blood	GoldenGate Cancer Panel I Array (Illumina Inc, USA) Validation using A PyroMark MD Pyrosequencing System (Qiagen) in replication cohort	No associations between maternal pre-pregnancy BMI and differentially methylated DNA at any CpG site No association of maternal pre-pregnancy BMI using pyrosequencing in replication cohort
Liu, et al, Environ Mol Mutagen 2014 223–230.	Boston Birth Cohort 309 Black (African American and Haitian), term newborns	cohort	USA	Cord blood	Illumina HumanMethylation27BeadChip	The methylation levels of 20 CpG sites were associated with maternal BMI. One CpG site (*ZCCHC10)* remained statistically significant after correction for multiple comparisons.
Sharp et al, Int J Epidemiol 2015; 44:1288-304.	ARIES (subset of ALSPAC) n-1018	cohort	UK	Cord blood	HumanMethylation 450 K	Compared with neonatal offspring of normal weight mothers, 28 and 1621 CpG sites were differentially methylated in offspring of obese and underweight mothers. A positive association, where higher methylation is associated with a body mass index (BMI) outside the normal range, was seen at 78.6% of

						the sites associated with obesity
Guenard et al, J Obes. 2013; 2013: 492170.	50 siblings aged 2 years 8 months to 24 years 11 months, , born before and after maternal bariatric surgery (25 BMS and 25 AMS offspring)	case/ control	Canada	Peripheral blood	Genome-wide methylation analysis using the Infinium HumanMethylation450 BeadChip	5698 differentially methylated genes between BMS and AMS offspring. Main differences in inflammatory and immune pathways

Studies using candidate gene approach

Study	Population	Design	Country	Tissue	Method	Findings
Gemma et al, Obesity 2009 ;17(5): 1032-9.	88 newborns: 57 newborns with appropriate weight for gestational age (AGA), 17 SGA, and 14 LGA	cohort	Argentina	Umbilical cord	PPARGC1A promoter After bisulphite treatment of umbilical cord genomic DNA, a real-time methylation-specific PCR was used to determine the promoter methylation status in selected CpGs	positive correlation between maternal BMI and PPARGC1A promoter methylation in umbilical cord (Pearson correlation coefficient r = 0.41, P = 0.0007)
Hoyo et al, Cancer Causes Control 2012;23:635-45	438 participants in Newborn Epigenetics STudy (NEST)	cohort	USA	Cord blood	Bisulphite sequencinc	Lower *IGF2* DMR methylation was associated with elevated plasma IGF2 protein concentrations, an association that was stronger in infants born to obese women. Elevated IGF2 concentrations were associated with higher birth weight
Soubry et al, BMC Mewd 2013; 11:29	79 newborns from the NEST cohort	cohort	USA	Cord blood	Bisulphite sequencing	Increase in DNA methylation at the IGF2 and H19 DMRs among newborns from obese mothers
Soubry et al, Int J Obes 2015;39: 650-7.	92 newborns from the NEST cohort	cohort	USA	Cord blood	Bisulphite pyrosequencing	Obesity in mothers was associated with an increase in methylation at the *PLAGL1* DMR β-coefficient +2.58 (s.e.=1.00; P=0.01) and a decrease at the *MEG* DMR (β-coefficient 3.42 (s.e.=1.69; P=0.04).
Burris et al, Epigenetics 2015; 10:913-21.	531 infants from Programming Research in Obesity, Growth Environment and Social Stress (PROGRESS) cohort	cohort	Mexico City	Cord blood	aryl-hydrocarbon receptor repressor (*AHRR*) DNA methylation by bisulphite sequencing	*AHRR* DNA methylation was positively associated with maternal BMI (*P* = 0.0009) *AHRR* DNA methylation was 2.1% higher in offspring of obese vs. normal weight mothers representing a third of the standard deviation differences in methylation

Table 4. Key points for future research

- *Molecular mechanisms*: Comprehensive experimental research is required into the epigenetic and other mechanisms linking maternal obesity to long term outcomes in the offspring. This will enable development of novel biomarkers and assist design of new intervention studies.

- *Lifestyle, nutritional and metabolic drivers:* Detailed information is needed on the specific maternal lifestyle (e.g. physical activity, smoking, other environmental stressors), nutritional and metabolic exposures that underpin effects of maternal obesity on offspring outcomes. This needs to be combined with information on whether there are critical periods during development when such exposures have their effects and whether any outcomes are sex-specific.

- *Causality*: Alongside mechanistic research, sophisticated observational studies are needed to obtain further insight into the (multiple) causalities of the observed associations. Such study designs include parent-offspring longitudinal cohorts, sib-pair analyses and the use of genetic variants and haplotypes as instrumental variables.

- *The need for new intervention studies*: There is a paucity of intervention studies focused on remediation of maternal obesity before and during pregnancy, or on moderation of the effects of maternal obesity on the offspring. With a deeper understanding of the underlying mechanisms, new interventions need to be designed and tested, with long-term follow-up of the offspring.